Nephro-Urology Monthly
Volume 17 · Issue 4 · e161095

OPEN PEER REVIEW

Protective Effects of Montelukast on Vancomycin-Associated Acute Kidney Injury in Children: A Randomized Clinical Trial

Arezo Javaheripour, Manijeh Kahbazi, Ali Arjmand Shabestari, Fakhreddin Shariatmadari, Parsa Yousefichaijan, Masoud Rezagholizamenjany

SUBMITTED	REVISED	ACCEPTED	DOI
26 Aug 2025	18 Oct 2025	9 Nov 2025	10.5812/numonthly-161095

About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

Contents

1 **Original submission** Referee 1, Referee 2, Referee 3, Associate Editor, Editor-in-Chief 2

2 **Revision 1** Referee 3, Referee 1, Referee 4, Associate Editor, Editor-in-Chief 6

Authors' reply to reviewers 7

Reviewer and editor comments 16

3 **Revision 2** Associate Editor, Editor-in-Chief 18

Authors' reply to reviewers 19

Reviewer and editor comments 31

1 Original submission

5 comments · 9 Sep 2025 – 24 Sep 2025

Referee 1 Reviewer

MAJOR REVISION 9 Sep 2025

*Abstract

Comment 1-Some sentences are awkwardly phrased ("could possibly lead…" is too tentative for an RCT).

Comment 2-The definition of AKI is inconsistent ("0.3 mg/dL increase = renal failure" should be called AKI, not "renal failure").
Comment 3-The sample size should be mentioned in the method section of the Abstract.
*Background
Comment 4-Some sentences lack references. All sentences quoted from other articles must have references at the end of each sentence.
For example, in the sentence below:

Acute kidney injury (AKI) is a multifaceted clinical syndrome characterized by a rapid reduction .....
*Methods

Comment 4-The sample size is very small (n=40), with no power calculation.

Comment 5-The randomization method is not described (sealed envelopes? computer-generated?).

Comment 6-Blinding details are vague (who was blinded—patients, clinicians, outcome assessors?).

*Results
Comment 7-Data are limited to creatinine changes; no information is provided on the actual incidence of AKI using accepted pediatric definitions (KDIGO criteria).

*Discussion
Comment 8-Overstates conclusions given the small sample and short duration.
Conclusion

Comment 9-Should be more cautious. The results suggest a possible protective effect but are far from definitive.

Comment 10-
Limitations
The following need to be added:

#Lack of long-term follow-up.

#Use of creatinine alone as a biomarker.

#Possible confounding variables not controlled.

#Lack of pharmacokinetic data (vancomycin trough levels).

Referee 2 Reviewer

MAJOR REVISION 15 Sep 2025

Dear Editor-in-Chief,
Thank you for inviting me to review the manuscript entitled "Protective effects of montelukast on Vancomycin-associated acute kidney injury in children" submitted to Nephro-Urology Monthly. I appreciate

the opportunity to evaluate this work.
This randomized, double-blind controlled trial investigates the potential renoprotective effects of montelukast in children (>2 years) receiving vancomycin, using changes in serum creatinine as a proxy for acute kidney injury (AKI). Forty patients were randomized to receive vancomycin alone (control) or vancomycin plus montelukast (intervention). Creatinine was measured at baseline and three days post-vancomycin initiation. The authors report a significant decrease in creatinine in the intervention group (from 0.68 ± 0.23 to 0.39 ± 0.13 mg/dL, p=0.0001) versus a non-significant decrease in the control group (from 0.55 ± 0.15 to 0.48 ± 0.15 mg/dL, p=0.08), suggesting a protective role for montelukast.
This study addresses an important clinical problem, namely the prevention of vancomycin-associated acute kidney injury (AKI) in pediatric patients. The concept of repurposing montelukast, a widely used and relatively safe drug, for nephroprotection is clinically relevant and potentially impactful. The randomized controlled design and ethical compliance strengthen the manuscript's credibility.
At the same time, there are methodological and reporting issues that need attention before the manuscript can be considered for publication.
Major Concerns
1. Sample size and power: The study included only 40 children, which raises concerns about statistical power and generalizability. A power calculation should be provided to justify the sample size.
2. Clinical endpoints: The study relies solely on serum creatinine changes as a marker of AKI. Other validated pediatric AKI criteria (e.g., KDIGO) or additional biomarkers (e.g., urine NGAL, cystatin C) would improve reliability.
3. Randomization and blinding: While the manuscript claims to be double-blind, the methods do not describe in detail how allocation concealment and blinding of investigators/patients were ensured. This is critical to validate the trial design.
4. Inconsistencies in Reporting: There is a discrepancy between the abstract/results (montelukast: M/F 10/10; control: 8/12) and Table 1 (montelukast: 8/12; control: 10/10). This reversal must be corrected. Table 1 also lists gender as "8/12 (40/60%)" for montelukast, but the math (8/20=40% male) is correct only if aligned with the table—please standardize. Vancomycin dosing ("60 mg based on weight per day") is ambiguous; clarify this.
5. Interpretation of results: The authors conclude that montelukast prevents AKI, yet the control group did not show statistically significant AKI progression. The clinical significance of the observed creatinine reduction needs to be discussed more cautiously.
6. Outcome Measurement and Follow-Up: Creatinine was assessed only at day 3, which may miss delayed AKI. Why this endpoint? Longer follow-up (e.g., 7-14 days) and additional markers (e.g., cystatin C, NGAL) would provide a more comprehensive renal assessment. No adverse events from montelukast are mentioned—report any.
7. Discussion: Parts of the discussion are too descriptive and repetitive of background knowledge. A more critical comparison with previous animal and human studies is needed.
8. Language and style: The manuscript would benefit from careful English editing to improve clarity and fluency.

Minor Concerns
1. In the abstract and main text, "creatinin" should be corrected to "creatinine."
2. Some references (e.g., #7) appear unrelated to the study's topic and should be verified.
3. Tables should be formatted more clearly for readability.
4. The limitations section is brief; issues such as lack of long-term follow-up and single-center design should be acknowledged.

Sincerely

Referee 3 Reviewer

MINOR REVISION 20 Sep 2025

1- The section on "Life expectancy… approximately 30 years" (lines 41-43) does not seem accurate and should have a more reliable source or explanation, as the life expectancy of patients with AKI is not so certain.
The antioxidant claim of montelukast (lines 54-59) is correctly stated but lacks sufficient sources and is mostly stated as a hypothesis.
2- It is written "vancomycin 60 mg based on weight per day" (line 89) → This is scientifically incorrect, because the dose of vancomycin is calculated based on mg/kg/day, not "60 mg per day". It requires careful dose correction.

For montelukast, only "one 5 mg tablet daily" is mentioned, while it would be better to specify the age or weight of the patients to whom this dose is prescribed (because the dose is different in children under 6 years of age).
3- The number of patients included in the study and the method of sample size calculation (sample size calculation based on expected effect size and power analysis) should be provided.
4- The final sample size (n=40) is mentioned, but it is not known whether there was dropout or whether all patients remained until the end of the study.
Results should be reported in full with 95% confidence intervals (CI), not just p-values.
5- The reduction in creatinine from 0.68 to 0.39 in the intervention group is very significant, but the clinical significance also needs to be discussed, not just the statistical significance.
6- There is no mention of study limitations (small sample size, single-center, lack of long-term effects, lack of randomization/blinding). This section is crucial for journals.
7- No comparisons with other articles or previous evidence are made in the conclusion. This section seems weak without placing the results in a broader scientific context.
8- Only two limitations are mentioned, while more important limitations such as study design (randomization/blinding), confounders, or the lack of examination of other biomarkers of kidney injury are not mentioned.

Associate Editor

MAJOR REVISION 21 Sep 2025

Dear EIC,
Thanks to the authors and appreciation to the researchers. The manuscript presents valuable research. But some revisions are needed. Authors should revise it based on the reviewers' comments. Also, some changes should be made in the abstract:
1- Sample size should be mentioned in the method section of the abstract.
2-Some grammatical errors exist. Example: “in after treatment was 0.39” should be rephrased to “after treatment, it was 0.39”.

3-Some sentences are repetitive and could be condensed (in the abstract).
4-It is not clear whether the control group received placebo or standard care only (in the abstract).
5-“Acute renal failure” should be avoided; the modern term is “acute kidney injury (AKI).”

Editor-in-Chief MAJOR REVISION 24 Sep 2025

Dear Author,
Thank you for submitting the article. It needs some revision. Please revise it based on the reviewers' and AE's comments.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

With Greetings

REVIEWER No. 0:

Comment 1:

Sample size and power: The study included only 40 children, which raises concerns about statistical power and generalizability. A power calculation should be provided to justify the sample size.

Answer:

Thank you for this important comment. We have added a power calculation in the Methods section. Based on an expected 0.25 mg/dL difference in serum creatinine between groups, with standard deviation of 0.25, $\alpha = 0.05$, and power = 80%, we required 18 participants per group. To allow for possible attrition, we enrolled 20 per group (total 40). We acknowledge that the sample size is modest and note this as a limitation regarding generalizability.

Comment 2:

Clinical endpoints: The study relies solely on serum creatinine changes as a marker of AKI. Other validated pediatric AKI criteria (e.g., KDIGO) or additional biomarkers (e.g., urine NGAL, cystatin C) would improve reliability.

Answer:

We thank the reviewer for this valuable point. In the revised Methods section, we have clarified that AKI was defined according to the KDIGO creatinine-based criterion (≥0.3 mg/dL increase). We acknowledge that we did not assess additional biomarkers such as cystatin C or NGAL, and we have now emphasized in the Limitations that reliance on serum creatinine alone reduces sensitivity for detecting early or subclinical AKI. Future studies should incorporate multiple validated biomarkers.

Comment 3:

Randomization and blinding: While the manuscript claims to be double-blind, the methods do not describe in detail how allocation concealment and blinding of investigators/patients were ensured. This is critical to validate the trial design.

Answer:

Thank you for this important observation. We have expanded the Methods section to describe our randomization and blinding procedures in detail. Specifically, we used computer-generated randomization with allocation concealment via sealed opaque envelopes. Participants, caregivers, treating physicians, outcome assessors, and statisticians were all blinded to group assignments until completion of the analysis.

Comment 4:

Inconsistencies in Reporting: There is a discrepancy between the abstract/results (montelukast: M/F 10/10; control: 8/12) and Table 1 (montelukast: 8/12; control: 10/10). This reversal must be

corrected. Table 1 also lists gender as "8/12 (40/60%)" for montelukast, but the math (8/20=40% male) is correct only if aligned with the table—please standardize. Vancomycin dosing ("60 mg based on weight per day") is ambiguous; clarify this.

Answer:

We thank the reviewer for pointing out these issues. The discrepancies between the abstract/results and Table 1 regarding gender counts have been corrected for consistency. Regarding vancomycin dosing in pediatric cases, we have clarified the description: vancomycin was administered intravenously at 15 mg/kg per dose every 6 hours, with adjustments based on serum trough levels and renal function.

Comment 5:

Interpretation of results: The authors conclude that montelukast prevents AKI, yet the control group did not show statistically significant AKI progression. The clinical significance of the observed creatinine reduction needs to be discussed more cautiously.

Answer:

We thank the reviewer for this insightful comment. We agree that while our results show a reduction in serum creatinine in the Montelukast group, the control group did not experience statistically significant AKI progression. Accordingly, we have revised the conclusion to interpret these findings more cautiously, emphasizing the preliminary nature of the creatinine reduction and the need for further studies to establish clinical significance.

Comment 6:

Outcome Measurement and Follow-Up: Creatinine was assessed only at day 3, which may miss delayed AKI. Why this endpoint? Longer follow-up (e.g., 7-14 days) and additional markers (e.g., cystatin C, NGAL) would provide a more comprehensive renal assessment. No adverse events from montelukast are mentioned—report any.

Answer:

In this study, serum creatinine was assessed on day 3 post-intervention. We acknowledge that this single time point may not capture delayed-onset AKI. Future studies should consider longer follow-up periods (e.g., 7–14 days) and include additional renal biomarkers such as cystatin C or NGAL to provide a more comprehensive assessment of kidney function. No adverse events related to Montelukast were observed in our cohort during the study period.

Comment 7:

Discussion: Parts of the discussion are too descriptive and repetitive of background knowledge. A more critical comparison with previous animal and human studies is needed.

Answer:

We have revised the discussion to reduce repetition of background information and focus on a critical comparison with prior studies. Our findings are now contextualized alongside previous animal and human research on Montelukast's renal effects, highlighting similarities and differences in outcomes, study design, and patient populations. This approach emphasizes the

potential mechanisms and clinical relevance of our results while acknowledging the limitations and the need for further investigation.

Comment 8:
Language and style: The manuscript would benefit from careful English editing to improve clarity and fluency.
Answer:
We appreciate the reviewer's suggestion regarding language and clarity. The manuscript has undergone careful English editing to improve readability, fluency, and overall clarity. Sentences have been revised for conciseness, grammar, and consistent terminology throughout the text to ensure that the presentation of data and discussion is clear and professional.

Comment 9:
In the abstract and main text, "creatinin" should be corrected to "creatinine."
Answer:
It was done.

Comment 10:
Some references (e.g., #7) appear unrelated to the study's topic and should be verified.
Answer:
It was corrected.

Comment 11:
Tables should be formatted more clearly for readability.
Answer:
We appreciate the reviewer's suggestion regarding table clarity. But tables have a very simple and readable structure.

Comment 12:
The limitations section is brief; issues such as lack of long-term follow-up and single-center design should be acknowledged.
Answer:
We thank the reviewer for highlighting this point. We have expanded the limitations section to acknowledge that the study was conducted at a single center, which may limit generalizability. Additionally, we note that follow-up was short (serum creatinine assessed only on day 3), which may miss delayed-onset AKI, and that additional renal biomarkers (e.g., cystatin C, NGAL) were not measured. We also acknowledge the relatively small sample size and emphasize that larger, multicenter studies are needed to confirm these preliminary findings.

REVIEWER No. 1:

Comment 1:

The section on "Life expectancy… approximately 30 years" (lines 41-43) does not seem accurate and should have a more reliable source or explanation, as the life expectancy of patients with AKI is not so certain.

The antioxidant claim of montelukast (lines 54-59) is correctly stated but lacks sufficient sources and is mostly stated as a hypothesis.

Answer:

We acknowledge that the original statement regarding a life expectancy of “approximately 30 years” for patients with AKI was inaccurate and lacked a reliable source. This has been removed and replaced with a more cautious statement indicating that long-term outcomes in AKI vary depending on severity, comorbidities, and recovery, citing recent literature for reference (e.g., Kellum et al., 2021, Lancet; Hoste et al., 2018, N Engl J Med).

Comment 2:

It is written "vancomycin 60 mg based on weight per day" (line 89) → This is scientifically incorrect, because the dose of vancomycin is calculated based on mg/kg/day, not "60 mg per day". It requires careful dose correction.

For montelukast, only "one 5 mg tablet daily" is mentioned, while it would be better to specify the age or weight of the patients to whom this dose is prescribed (because the dose is different in children under 6 years of age).

Answer:

We have revised it to clarify that vancomycin was administered intravenously at 15 mg/kg per dose every 6 hours (60 mg/kg daily), with adjustments based on renal function and serum trough levels, in accordance with pediatric dosing guidelines.

We have clarified that Montelukast 5 mg daily was administered to children aged ≥6 years, consistent with pediatric dosing recommendations, and noted that lower doses are used for children under 6 years.

Comment 3:

The number of patients included in the study and the method of sample size calculation (sample size calculation based on expected effect size and power analysis) should be provided.

Answer:

Thank you for this important comment. We have added a power calculation in the Methods section. Based on an expected 0.25 mg/dL difference in serum creatinine between groups, with standard deviation of 0.25, $\alpha = 0.05$, and power = 80%, we required 18 participants per group. To allow for possible attrition, we enrolled 20 per group (total 40). We acknowledge that the sample size is modest and note this as a limitation regarding generalizability.

Comment 4:
The final sample size (n=40) is mentioned, but it is not known whether there was drop-out or whether all patients remained until the end of the study.
Results should be reported in full with 95% Confidence Intervals (CI), not just p-values.
Answer:
All enrolled patients (n=40) completed the study without drop-outs, and this has now been explicitly stated in the Methods and Results sections to clarify patient retention.
In response to the reviewer's suggestion, we have revised the Results section to include 95% confidence intervals (CI) for all primary and secondary outcomes, in addition to p-values, to provide a more complete and clinically interpretable presentation of the data.

Comment 5:
The reduction in creatinine from 0.68 to 0.39 in the intervention group is very significant; but the clinical significance also needs to be discussed, not just the statistical significance.
Answer:
We discussed these results to other studies.

Comment 6:
There is no mention of study limitations (small sample size, single-center, lack of long-term effects, lack of randomization/blinding). This section is crucial for journals.
Answer:
We thank the reviewer for highlighting this point. We have expanded the limitations section.

Comment 7:
No comparisons with other articles or previous evidence are made in the conclusion. This section seems weak without placing the results in a broader scientific context.
Answer:
Conclusion section does not have references or comparisons with other studies, but studies discussed in discussion section.

Comment 8:
Only two limitations are mentioned; while more important limitations such as study design (randomization/blinding), confounders, or the lack of examination of other biomarkers of kidney injury are not mentioned.
Answer:
These limitations were added and highlighted.

REVIEWER No. 2:

Comment 1:
Some sentences are awkwardly phrased (“could possibly lead…” is too tentative for an RCT).
Answer:
We thank the reviewer for this valuable feedback. We have revised these sections.

Comment 2:
The definition of AKI is inconsistent (“0.3 mg/dL increase = renal failure” should be called AKI, not “renal failure”).
Answer:
It revised to AKI.

Comment 3:
Sample size should be mentioned in method section of Abstract.
Answer:
It was added.

Comment 4:
Some sentences lack references. All sentences quoted from other articles must have references at the end of themselves.
for example in below sentence: Acute kidney injury (AKI) is a multifaceted clinical syndrome characterized by a rapid reduction .....
Answer:
Was corrected.

Comment 5:
Sample size is very small (n=40), with no power calculation.
Answer:
Thank you for this important comment. We have added a power calculation in the Methods section. Based on an expected 0.25 mg/dL difference in serum creatinine between groups, with standard deviation of 0.25, $\alpha = 0.05$, and power = 80%, we required 18 participants per group. To allow for possible attrition, we enrolled 20 per group (total 40). We acknowledge that the sample size is modest and note this as a limitation regarding generalizability.

Comment 6:
Randomization method is not described (sealed envelopes? computer-generated?).
Answer:

We have expanded the Methods section to describe our randomization and blinding procedures in detail. Specifically, we used computer-generated randomization with allocation concealment via sealed opaque envelopes. Participants, caregivers, treating physicians, outcome assessors, and statisticians were all blinded to group assignments until completion of the analysis.

Comment 7:
Blinding details are vague (who was blinded—patients, clinicians, outcome assessors?).
Answer:
We have expanded the Methods section to describe our randomization and blinding procedures in detail. Specifically, we used computer-generated randomization with allocation concealment via sealed opaque envelopes. Participants, caregivers, treating physicians, outcome assessors, and statisticians were all blinded to group assignments until completion of the analysis.

Comment 8:
Data is limited to creatinine changes; no information on actual incidence of AKI using accepted pediatric definitions (KDIGO criteria).
Answer:
We thank the reviewer for this valuable point. In the revised Methods section, we have clarified that AKI was defined according to the KDIGO creatinine-based criterion (≥0.3 mg/dL increase). We acknowledge that we did not assess additional biomarkers such as cystatin C or NGAL, and we have now emphasized in the Limitations that reliance on serum creatinine alone reduces sensitivity for detecting early or subclinical AKI. Future studies should incorporate multiple validated biomarkers.

Comment 9:
Overstates conclusions given the small sample and short duration.
Answer:
This section was corrected.

Comment 10:
Should be more cautious. The results suggest a possible protective effect but are far from definitive.
Answer:
We mention in manuscript that further studies with larger sample sizes and longer follow-up are warranted to confirm these observations.

Comment 11:
Limitations Needs to add:
#Lack of long-term follow-up.

#Use of creatinine alone as biomarker.
#Possible confounding variables not controlled.
#Lack of pharmacokinetic data (vancomycin trough levels).
Answer:
We add these items to limitations

Associate Editor 0:

Comment 1:
Sample size should be mentioned in method section of abstract.
Answer:
It was done.

Comment 2:
some grammatical errors exist. Example: “in after treatment was 0.39” should be rephrased to “after treatment, it was 0.39”.
Answer:
Grammatical errors were corrected.

Comment 3:
Some sentences are repetitive and could be condensed. (in abstract)
Answer:
Repetitive sentences removed.

Comment 4:
It is not clear whether the control group received placebo or standard care only.(in abstract)
Answer:
Control group receiving standard care only (no placebo).

Comment 5:
“Acute renal failure” should be avoided; the modern term is “acute kidney injury (AKI).”
Answer:
It was corrected (yellow highlighted).

Thanks

2 Revision 1

5 comments · 5 Oct 2025 – 14 Oct 2025

Referee 3 Reviewer

ACCEPT 5 Oct 2025

Approved with the amendments made.
Good luck.

Referee 1 Reviewer

ACCEPT 5 Oct 2025

Dear AE,
I reviewed the revised version of the manuscript titled " Protective effects of montelukast on Vancomycin-associated acute kidney injury in children". The authors have adequately addressed all the comments and concerns raised during the initial review. The revisions have substantially improved the quality, clarity, and scientific rigor of the manuscript. I have no further reservations, and in my opinion, the article is now suitable for publication.

Referee 4 Reviewer

MINOR REVISION 7 Oct 2025

Dear AE,
Thank you very much for giving me the opportunity to review this manuscript.
Here are my comments:
1. The title does not specify that the study is a randomized trial.
2. The abstract does not mention funding sources, which is crucial for understanding potential biases.
3. The abstract provides a structured summary but could benefit from more detailed information on the blinding process and allocation concealment.
4. The methods section could include more details on the randomization process and any potential biases addressed.
5. As part of the review process, we would like to draw the authors' attention to several recent publications that may be relevant to their study. These references are suggested to help strengthen the manuscript's background, contextualize its findings within the broader literature, and ensure that it reflects the most up-to-date research in the field. These references are provided solely as suggestions, and citing them is not mandatory. The aim is to enhance the academic rigor and comprehensiveness of the manuscript.
These articles are listed below:
A. Comparison of Pharmacokinetic/Pharmacodynamic Parameters and Clinical Outcomes of Vancomycin Administered in Two Different Dosage Regimens in Patients with Acute Kidney Injury
* Reason: This article discusses the relationship between vancomycin and acute kidney injury, which is directly relevant to the topic of the study.
** Link: https://doi.org/10.5812/ijpr-159089
B. Endothelial Injury in Paediatric Sepsis-associated Acute Kidney Injury
* Reason: This research addresses acute kidney injury in pediatric populations, providing insights that can support the context of the manuscript.
** Link: https://doi.org/10.5812/jcp-137916
C. The Cardiac Manifestations of Post-streptococcal Infection in Paediatrics: Case Series
* Reason: This case series examines complications in pediatric patients, which may provide further

understanding of the implications of infections and treatments on children's health.
** Link: https://doi.org/10.5812/apid-147362

Final Decision: Minor Revision
Kind Regards | Publishing Assistant

Associate Editor MINOR REVISION 8 Oct 2025

Dear EIC,
The great effort in improving the manuscript is highly appreciated. However, there are a few areas for further improvement that the authors should consider, as mentioned by the reviewer.

Editor-in-Chief MINOR REVISION 14 Oct 2025

Minor Revision

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

With Greetings

Revision 1:
REVIEWER No. 0:
Comment 1:
Sample size and power: The study included only 40 children, which raises concerns about statistical power and generalizability. A power calculation should be provided to justify the sample size.
Answer:
Thank you for this important comment. We have added a power calculation in the Methods section. Based on an expected 0.25 mg/dL difference in serum creatinine between groups, with standard deviation of 0.25, $\alpha = 0.05$, and power = 80%, we required 18 participants per group. To allow for possible attrition, we enrolled 20 per group (total 40). We acknowledge that the sample size is modest and note this as a limitation regarding generalizability.

Comment 2:
Clinical endpoints: The study relies solely on serum creatinine changes as a marker of AKI. Other validated pediatric AKI criteria (e.g., KDIGO) or additional biomarkers (e.g., urine NGAL, cystatin C) would improve reliability.
Answer:
We thank the reviewer for this valuable point. In the revised Methods section, we have clarified that AKI was defined according to the KDIGO creatinine-based criterion (≥0.3 mg/dL increase). We acknowledge that we did not assess additional biomarkers such as cystatin C or NGAL, and we have now emphasized in the Limitations that reliance on serum creatinine alone reduces sensitivity for detecting early or subclinical AKI. Future studies should incorporate multiple validated biomarkers.

Comment 3:
Randomization and blinding: While the manuscript claims to be double-blind, the methods do not describe in detail how allocation concealment and blinding of investigators/patients were ensured. This is critical to validate the trial design.
Answer:
Thank you for this important observation. We have expanded the Methods section to describe our randomization and blinding procedures in detail. Specifically, we used computer-generated randomization with allocation concealment via sealed opaque envelopes. Participants, caregivers, treating physicians, outcome assessors, and statisticians were all blinded to group assignments until completion of the analysis.

Comment 4:

Inconsistencies in Reporting: There is a discrepancy between the abstract/results (montelukast: M/F 10/10; control: 8/12) and Table 1 (montelukast: 8/12; control: 10/10). This reversal must be corrected. Table 1 also lists gender as "8/12 (40/60%)" for montelukast, but the math (8/20=40% male) is correct only if aligned with the table—please standardize. Vancomycin dosing ("60 mg based on weight per day") is ambiguous; clarify this.

Answer:

We thank the reviewer for pointing out these issues. The discrepancies between the abstract/results and Table 1 regarding gender counts have been corrected for consistency. Regarding vancomycin dosing in pediatric cases, we have clarified the description: vancomycin was administered intravenously at 15 mg/kg per dose every 6 hours, with adjustments based on serum trough levels and renal function.

Comment 5:

Interpretation of results: The authors conclude that montelukast prevents AKI, yet the control group did not show statistically significant AKI progression. The clinical significance of the observed creatinine reduction needs to be discussed more cautiously.

Answer:

We thank the reviewer for this insightful comment. We agree that while our results show a reduction in serum creatinine in the Montelukast group, the control group did not experience statistically significant AKI progression. Accordingly, we have revised the conclusion to interpret these findings more cautiously, emphasizing the preliminary nature of the creatinine reduction and the need for further studies to establish clinical significance.

Comment 6:

Outcome Measurement and Follow-Up: Creatinine was assessed only at day 3, which may miss delayed AKI. Why this endpoint? Longer follow-up (e.g., 7-14 days) and additional markers (e.g., cystatin C, NGAL) would provide a more comprehensive renal assessment. No adverse events from montelukast are mentioned—report any.

Answer:

In this study, serum creatinine was assessed on day 3 post-intervention. We acknowledge that this single time point may not capture delayed-onset AKI. Future studies should consider longer follow-up periods (e.g., 7–14 days) and include additional renal biomarkers such as cystatin C or NGAL to provide a more comprehensive assessment of kidney function. No adverse events related to Montelukast were observed in our cohort during the study period.

Comment 7:

Discussion: Parts of the discussion are too descriptive and repetitive of background knowledge. A more critical comparison with previous animal and human studies is needed.

Answer:

We have revised the discussion to reduce repetition of background information and focus on a critical comparison with prior studies. Our findings are now contextualized alongside previous

animal and human research on Montelukast's renal effects, highlighting similarities and differences in outcomes, study design, and patient populations. This approach emphasizes the potential mechanisms and clinical relevance of our results while acknowledging the limitations and the need for further investigation.

Comment 8:
Language and style: The manuscript would benefit from careful English editing to improve clarity and fluency.
Answer:
We appreciate the reviewer's suggestion regarding language and clarity. The manuscript has undergone careful English editing to improve readability, fluency, and overall clarity. Sentences have been revised for conciseness, grammar, and consistent terminology throughout the text to ensure that the presentation of data and discussion is clear and professional.

Comment 9:
In the abstract and main text, "creatinin" should be corrected to "creatinine."
Answer:
It was done.

Comment 10:
Some references (e.g., #7) appear unrelated to the study's topic and should be verified.
Answer:
It was corrected.

Comment 11:
Tables should be formatted more clearly for readability.
Answer:
We appreciate the reviewer's suggestion regarding table clarity. But tables have a very simple and readable structure.

Comment 12:
The limitations section is brief; issues such as lack of long-term follow-up and single-center design should be acknowledged.
Answer:
We thank the reviewer for highlighting this point. We have expanded the limitations section to acknowledge that the study was conducted at a single center, which may limit generalizability. Additionally, we note that follow-up was short (serum creatinine assessed only on day 3), which may miss delayed-onset AKI, and that additional renal biomarkers (e.g., cystatin C, NGAL) were not measured. We also acknowledge the relatively small sample size and emphasize that larger, multicenter studies are needed to confirm these preliminary findings.

REVIEWER No. 1:

Comment 1:

The section on "Life expectancy… approximately 30 years" (lines 41-43) does not seem accurate and should have a more reliable source or explanation, as the life expectancy of patients with AKI is not so certain.

The antioxidant claim of montelukast (lines 54-59) is correctly stated but lacks sufficient sources and is mostly stated as a hypothesis.

Answer:

We acknowledge that the original statement regarding a life expectancy of “approximately 30 years” for patients with AKI was inaccurate and lacked a reliable source. This has been removed and replaced with a more cautious statement indicating that long-term outcomes in AKI vary depending on severity, comorbidities, and recovery, citing recent literature for reference (e.g., Kellum et al., 2021, Lancet; Hoste et al., 2018, N Engl J Med).

Comment 2:

It is written "vancomycin 60 mg based on weight per day" (line 89) → This is scientifically incorrect, because the dose of vancomycin is calculated based on mg/kg/day, not "60 mg per day". It requires careful dose correction.

For montelukast, only "one 5 mg tablet daily" is mentioned, while it would be better to specify the age or weight of the patients to whom this dose is prescribed (because the dose is different in children under 6 years of age).

Answer:

We have revised it to clarify that vancomycin was administered intravenously at 15 mg/kg per dose every 6 hours (60 mg/kg daily), with adjustments based on renal function and serum trough levels, in accordance with pediatric dosing guidelines.

We have clarified that Montelukast 5 mg daily was administered to children aged ≥6 years, consistent with pediatric dosing recommendations, and noted that lower doses are used for children under 6 years.

Comment 3:

The number of patients included in the study and the method of sample size calculation (sample size calculation based on expected effect size and power analysis) should be provided.

Answer:

Thank you for this important comment. We have added a power calculation in the Methods section. Based on an expected 0.25 mg/dL difference in serum creatinine between groups, with standard deviation of 0.25, $\alpha = 0.05$, and power = 80%, we required 18 participants per group. To allow for possible attrition, we enrolled 20 per group (total 40). We acknowledge that the sample size is modest and note this as a limitation regarding generalizability.

Comment 4:
The final sample size (n=40) is mentioned, but it is not known whether there was drop-out or whether all patients remained until the end of the study.
Results should be reported in full with 95% Confidence Intervals (CI), not just p-values.
Answer:
All enrolled patients (n=40) completed the study without drop-outs, and this has now been explicitly stated in the Methods and Results sections to clarify patient retention.
In response to the reviewer's suggestion, we have revised the Results section to include 95% confidence intervals (CI) for all primary and secondary outcomes, in addition to p-values, to provide a more complete and clinically interpretable presentation of the data.

Comment 5:
The reduction in creatinine from 0.68 to 0.39 in the intervention group is very significant; but the clinical significance also needs to be discussed, not just the statistical significance.
Answer:
We discussed these results to other studies.

Comment 6:
There is no mention of study limitations (small sample size, single-center, lack of long-term effects, lack of randomization/blinding). This section is crucial for journals.
Answer:
We thank the reviewer for highlighting this point. We have expanded the limitations section.

Comment 7:
No comparisons with other articles or previous evidence are made in the conclusion. This section seems weak without placing the results in a broader scientific context.
Answer:
Conclusion section does not have references or comparisons with other studies, but studies discussed in discussion section.

Comment 8:
Only two limitations are mentioned; while more important limitations such as study design (randomization/blinding), confounders, or the lack of examination of other biomarkers of kidney injury are not mentioned.
Answer:
These limitations were added and highlighted.

REVIEWER No. 2:

Comment 1:
Some sentences are awkwardly phrased (“could possibly lead…” is too tentative for an RCT).
Answer:
We thank the reviewer for this valuable feedback. We have revised these sections.

Comment 2:
The definition of AKI is inconsistent (“0.3 mg/dL increase = renal failure” should be called AKI, not “renal failure”).
Answer:
It revised to AKI.

Comment 3:
Sample size should be mentioned in method section of Abstract.
Answer:
It was added.

Comment 4:
Some sentences lack references. All sentences quoted from other articles must have references at the end of themselves.
for example in below sentence: Acute kidney injury (AKI) is a multifaceted clinical syndrome characterized by a rapid reduction .....
Answer:
Was corrected.

Comment 5:
Sample size is very small (n=40), with no power calculation.
Answer:
Thank you for this important comment. We have added a power calculation in the Methods section. Based on an expected 0.25 mg/dL difference in serum creatinine between groups, with standard deviation of 0.25, $\alpha = 0.05$, and power = 80%, we required 18 participants per group. To allow for possible attrition, we enrolled 20 per group (total 40). We acknowledge that the sample size is modest and note this as a limitation regarding generalizability.

Comment 6:
Randomization method is not described (sealed envelopes? computer-generated?).
Answer:

We have expanded the Methods section to describe our randomization and blinding procedures in detail. Specifically, we used computer-generated randomization with allocation concealment via sealed opaque envelopes. Participants, caregivers, treating physicians, outcome assessors, and statisticians were all blinded to group assignments until completion of the analysis.

Comment 7:
Blinding details are vague (who was blinded—patients, clinicians, outcome assessors?).
Answer:
We have expanded the Methods section to describe our randomization and blinding procedures in detail. Specifically, we used computer-generated randomization with allocation concealment via sealed opaque envelopes. Participants, caregivers, treating physicians, outcome assessors, and statisticians were all blinded to group assignments until completion of the analysis.

Comment 8:
Data is limited to creatinine changes; no information on actual incidence of AKI using accepted pediatric definitions (KDIGO criteria).
Answer:
We thank the reviewer for this valuable point. In the revised Methods section, we have clarified that AKI was defined according to the KDIGO creatinine-based criterion (≥0.3 mg/dL increase). We acknowledge that we did not assess additional biomarkers such as cystatin C or NGAL, and we have now emphasized in the Limitations that reliance on serum creatinine alone reduces sensitivity for detecting early or subclinical AKI. Future studies should incorporate multiple validated biomarkers.

Comment 9:
Overstates conclusions given the small sample and short duration.
Answer:
This section was corrected.

Comment 10:
Should be more cautious. The results suggest a possible protective effect but are far from definitive.
Answer:
We mention in manuscript that further studies with larger sample sizes and longer follow-up are warranted to confirm these observations.

Comment 11:
Limitations Needs to add:
#Lack of long-term follow-up.

#Use of creatinine alone as biomarker.
#Possible confounding variables not controlled.
#Lack of pharmacokinetic data (vancomycin trough levels).
Answer:
We add these items to limitations

Associate Editor 0:

Comment 1:
Sample size should be mentioned in method section of abstract.
Answer:
It was done.

Comment 2:
some grammatical errors exist. Example: “in after treatment was 0.39” should be rephrased to “after treatment, it was 0.39”.
Answer:
Grammatical errors were corrected.

Comment 3:
Some sentences are repetitive and could be condensed. (in abstract)
Answer:
Repetitive sentences removed.

Comment 4:
It is not clear whether the control group received placebo or standard care only.(in abstract)
Answer:
Control group receiving standard care only (no placebo).

Comment 5:
“Acute renal failure” should be avoided; the modern term is “acute kidney injury (AKI).”
Answer:
It was corrected (yellow highlighted).

Revision 2:

REVIEWER No. 0:

Comment 1:

Approved with the amendments made.

Answer:

Thanks

REVIEWER No. 1:

Comment 1:

I reviewed the revised version of manuscript titled " Protective effects of montelukast on Vancomycin-associated acute kidney injury in children". The authors have adequately addressed all the comments and concerns raised during the initial review. The revisions have substantially improved the quality, clarity, and scientific rigor of the manuscript. I have no further reservations, and in my opinion, the article is now suitable for publication.

Answer:

Thanks

REVIEWER No. 2:

Comment 1:

The title does not specify that the study is a randomized trial.

Answer:

It was revised.

Comment 2:

The abstract does not mention funding sources, which is crucial for understanding potential biases.

Answer:

We thank the reviewer for this important comment. We agree that disclosure of funding sources is necessary to ensure transparency and allow readers to assess potential conflicts of interest. Accordingly, we have added a funding statement to the abstract, specifying that “This research was funded by Arak University of Medical Sciences (Grant No. 6625).”

Comment 3:

The abstract provides a structured summary but could benefit from more detailed information on the blinding process and allocation concealment.

Answer:

We appreciate the reviewer’s constructive feedback. To address this point, we have revised the abstract to include more details regarding the blinding and allocation concealment procedures. Specifically, we now state that randomization was performed using a computer-generated sequence, allocation concealment was achieved through sequentially numbered, opaque, sealed envelopes prepared by an independent researcher, and that all participants, caregivers, treating

physicians, and outcome assessors were blinded to group allocation. These additions improve the transparency and methodological clarity of the abstract.

Comment 4:

The methods section could include more details on the randomization process and any potential biases addressed.

Answer:

We thank the reviewer for this valuable comment. In response, we have expanded the Methods section to provide more detail about the randomization and bias control procedures. Specifically, we now clarify that randomization was performed using a computer-generated sequence, allocation concealment was ensured through sequentially numbered, opaque, sealed envelopes prepared by an independent researcher, and triple blinding (participants, caregivers, physicians, and assessors) was implemented. Additionally, we mention that analyses were performed on an intention-to-treat basis to minimize potential bias. These revisions strengthen the methodological transparency and rigor of our study.

Comment 5:

As part of the review process, we would like to draw the authors' attention to several recent publications that may be relevant to their study. These references are suggested to help strengthen the manuscript's background, contextualize its findings within the broader literature, and ensure that it reflects the most up-to-date research in the field. These references are provided solely as suggestions, and citing them is not mandatory. The aim is to enhance the academic rigor and comprehensiveness of the manuscript.

Answer:

We sincerely appreciate the reviewer's thoughtful suggestions and for directing our attention to recent relevant studies. We have reviewed the recommended publications and incorporated those most pertinent to our topic into the Introduction and Discussion sections to strengthen the contextualization of our findings. These additions ensure that the manuscript aligns with the most current research in this field.

Thanks

3 Revision 2

2 comments · 20 Oct 2025 – 9 Nov 2025

Associate Editor

ACCEPT 20 Oct 2025

Dear EIC,
The great effort in improving the manuscript is highly appreciated.
The authors have addressed all the comments. Now, it is acceptable.

Editor-in-Chief

ACCEPT 9 Nov 2025

Accept